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CARBOHYDRATE RECOGNITION : ENANTIOSELECTIVE SPIROBIFLUORENE DIPHOSPHONATE RECEPTORS

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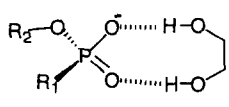
Abstract: The mono- and bis-tetrabutylammonium salts of 2-ethyl-spirobifluorene monophosphonate and (±) 2,2'-diethyl-7,7'-didodecyloxy-spirobifluorene diphosphonate respectively, were synthesized and shown to bind strongly to a series of 1-*O*-octylglycosides in CD_3CN. © 1997 Elsevier Science Ltd.

The design of artificial receptors that bind strongly and selectively to carbohydrate derivatives continues to be a very active area in bioorganic chemistry.[1] Several different strategies have been adopted in which hydrogen bonding groups are held within a macrocyclic or acyclic framework.[2-5] In general these receptors bind carbohydrate derivatives with modest affinity in non-polar organic solvents.[6] Our approach to improving the affinity of artificial carbohydrate receptors has been to exploit the strong association of 1,2- and 1,3-diols with anionic functional groups such as carboxylate and phosphonate.[7] The exact nature of the hydrogen bonding interaction may be one of three types as depicted below.[8]



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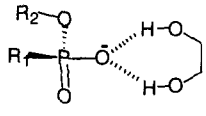

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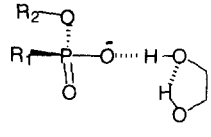

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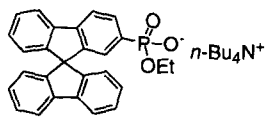
We earlier showed that relatively flexible diphosphonates bind strongly but with modest selectivity to alkylglycosides.[9-12] A key to improving the recognition properties of the carbohydrate receptors lies in increasing their rigidity and in providing a chiral disposition of the binding groups. In this paper we report the synthesis of monotopic and ditopic spirobifluorene phosphonates **4** and **5** and their *enantioselective* association with various glycosides in CD_3CN.



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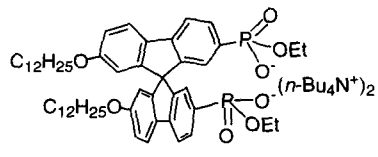

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The synthesis of the monotopic receptor **4** involved treatment of 2-bromofluorenone with 2-lithiobiphenyl followed by acid catalyzed cyclization of the resulting alcohol to give 2-bromospirobifluorene. This was phosphonylated[13] using diethyl phosphite and triethylamine in the presence of $Pd(PPh_3)_4$, to give diethyl 2-spirobifluorene phosphonate which was then monodeethylated in ammonia–saturated methanol at

150 °C,[14] and converted to the *n*-Bu_4N^+ salt by cation exchange (Amberlite H^+ and *n*-Bu_4N^+).[15] The bis tetrabutylammonium salt of diphosphonate **5** was prepared by an analogous route starting from 2,2'-dibromo-7,7'-didodecyloxy-spirobifluorene.[16]

The binding of monophosphonate **4** with different glycosides was studied by ^1H NMR spectroscopy by keeping the total glycoside concentration constant and gradually increasing the receptor concentration. Binding resulted in large downfield shifts of the O*H* protons (~2.7 ppm) and small upfield shifts of the glycoside C*H*(OH) protons (~0.1ppm). There were small shifts of the receptor ArC*H* protons and a very large downfield shift of the ^{31}P signal (2.4 ppm). The titration curves (see Figure 1A for 1-*O*-octyl-β-D-glucoside with **4**) were analysed by non-linear regression methods[17] and the 1:1 association constants are displayed in Table 1.[18] There is little discrimination among the different glycosides. The 1:1 stoichiometry of these adducts was confirmed from Job plots using glycoside 1-C*H*, 2-O*H* and receptor ^{31}P signals, all of which gave maxima at mole fraction [glycoside]/[glycoside + **4**] = 0.5 (Figure 1B). The results with **4** indicated that

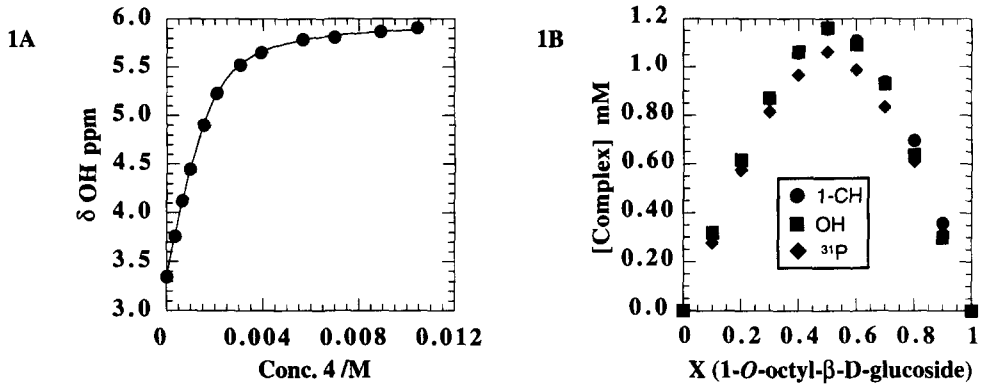

Figure 1A. Plot of the 2-O*H* signal of 1-*O*-octyl-β-D-glucoside ($[c]_0$ = 1.8 mM) vs. [**4**] and the 1:1 fitted curve ($K_a \approx 3.2 \times 10^3$ M^{-1}). **1B.** Job plot for the same host-guest pair ([glycoside] + [**4**] = 3.2 mM) using glycoside (O*H* ■, 1-C*H* ●) and receptor (^{31}P ◆) signals showing 1:1 complex formation.

two anionic phosphonates on a spirobifluorene spacer, as in **5**, might simultaneously bind to all four OH groups of the glycoside resulting in very strong association. A calculated structure for the complex of 1-*O*-methyl-β-D-glucoside and 2,2'-dimethyl-spirobifluorene diphosphonate is shown in Figure 2B.[19] Titrations were initially carried out with (±)**5** in the same way as described for **4**. Binding was accompanied by large downfield and small-to-moderate upfield shifts of the glycoside O*H* and 1-C*H* signals, respectively. Since the O*H* resonances showed line broadening, binding was monitored by following the upfield shift of the glycoside 1-C*H* as a function of receptor concentration. Curve fitting[20] gave "apparent K_a's" ranging from 2.4–4.7 × 10^4 M^{-1} (Table 1). In the case of the β-octylglucosides, the upfield shift of the 1-C*H* (~ 0.6 ppm) is >5-fold larger than with **4**, strongly suggesting that coordination by both phosphonate groups forces the sugar to lie close to the aromatic rings in **5**, as shown in Figure 2A.[19] A 1:1 stoichiometry for the complexes between 1-*O*-octyl-α-D-glucoside and **5** was confirmed from a Job plot.

In order to determine *enantioselective* binding, titrations were also performed by keeping the concentration of **5** constant and varying the glycoside concentration. In all titrations with glycosides, except

Table 1. $K_a^{a,b}$ (M^{-1}), K_{E1}/K_{E2} and $\Delta\delta$ (ppm) of binding of glycosides with **4** and **5** in CD_3CN at 20 °C

Substrate	**4** /10^3[c]	$(\Delta\delta)^d$	**5** /10^4[e]	$(\Delta\delta)^d$	K_{E1}/K_{E2}[f]	$(\Delta\delta)^{E1,E2}$[f]
1-*O*-octyl-β-D-glucopyranoside	3.22	(0.09)	4.70	(~0.60)[g]	5.10	(0.29, 0.13)
1-*O*-octyl-α-D-glucopyranoside	3.15	(0.08)	2.40	(0.19)	1.40	(0.12, 0.10)
1-*S*-octyl-β-D-glucopyranoside	3.97	(0.10)	>5.00	(~0.60)[g]	3.90	(0.27, 0.16)
1-*O*-octyl-β-D-galactopyranoside	3.11	(0.11)	4.51	(0.34)	0.54	(0.30, 0.18)
1-*O*-octyl-α-D-mannopyranoside	2.86	(0.07)	2.50	(0.14)	1.00	(0.09, 0.09)

[a]All K_a's are the mean of at least two determinations. [b]Errors for K_a's less than 10^4 were estimated to be ~10%; for K_a's above 10^4, ~ 20%. [c]Downfield shifts of the 2- and 3-O*H* 's were used. [d]$\Delta\delta$ of the glycoside 1-C*H* on complex formation. [e]K_a's treated as average for ± **5** and the glycoside. [f]$\Delta\delta^{E1,E2}$ = ([$\delta 5^{E1}$:glycoside–$\delta 5$], [$\delta 5^{E2}$:glycoside–$\delta 5$]). [g]Estimated changes in chemical shift due to peak overlap.

1-*O*-octyl-α-D-mannoside, receptor signals in the ^1H NMR spectrum separated into two sets, indicating possible differences in the binding of enantiomeric forms of **5** (designated E1 and E2) to the homochiral glycoside. Maximum splitting was observed for the 1,1'-C*H* doublets and this effect was quite large for the β-octylglucosides but modest for the galactoside and α-glucoside. In the case of the octyl-β-D-glucoside, the 8, 8'-ArC*H* doublet also separates and moves ~0.1 and ~0.05 ppm upfield. The plot of the chemical shifts of the 1,1'-ArC*H* of **5** vs. concentration of 1-*O*-octyl-β-D-glucoside is shown in Figure 2B. We have used the competitive method of Whitlock to calculate the ratio of association constants for the enantiomeric receptors (K_{E1}/K_{E2}) from δ^{E1}, δ^{E2}, and δ's of the [5^{E1}:glycoside] and [5^{E2}:glycoside] complexes.[21] Arbitrarily, the enantiomer which displays greater chemical shift on binding has been designated as E1. The ratio is ~ 5 for 1-*O*-octyl-β-D-glucoside, ~ 4 for 1-*S*-octyl-β-D-glucoside and 0.5, 1.4 and 1.0 for 1-*O*-octyl-β-D-galactoside,

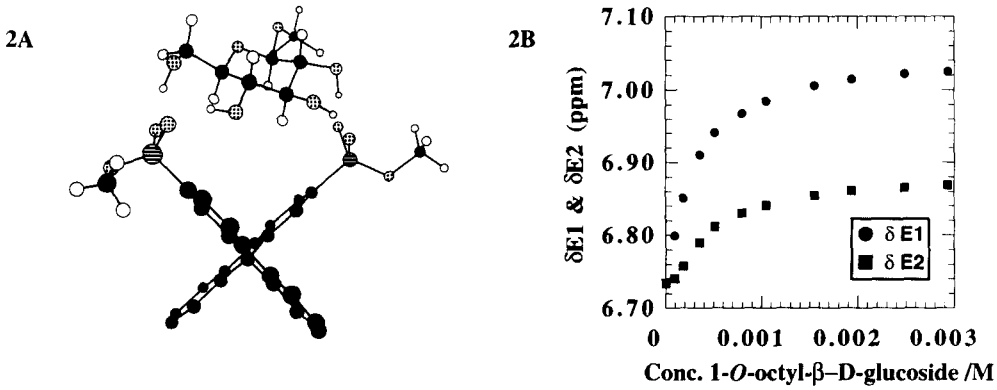

Figure 2A. Calculated structure of the complex between 2,2'-dimethyl-spirobifluorene diphosphonate and 1-*O*-methyl-β-D-glucoside.[19] **2B.** Plot of the chemical shifts of the 1,1' Ar-C*H*'s of the enantiomers of **5** ($[5]_0$ = 0.40 mM) vs. increasing glucoside concentration.

1-*O*-octyl-α-D-glucoside and 1.0 for 1-*O*-octyl-α-D mannoside, respectively. This result implies that the purified enantiomers of **5** would bind *enantioselectively* to the D- and L-glycosides by the same ratio.[22] The enantioselectivity is greatest for glycosides which do not have axial substituents at the 1- and 2- positions.

Also, in the case of the glucosides, the enantiomer which shows a larger chemical shift change is the one which has greater binding affinity and the reverse is true for the β-galactoside.

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18. Self association of the glycosides as well as **4** and **5** was deemed negligible from ^{1}H and ^{31}P NMR dilution studies and VPO experiments in acetonitrile in the range (5–25 mM).
19. Calculated (excluding counterions and solvent) using MM2*, MacroModel v. 3.5.
20. All titration curves were fitted to a 1:1 binding scheme. "Apparent K_a's" obtained this way are true K_a's when both enantiomers have identical affinities for the glycoside. Since differences in affinity are small for the majority of glycosides, K_a's calculated this way reflect the *average* association constants.
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$$\frac{K_{E1}}{K_{E2}} = \frac{f_{E1}}{f_{E2}} \times \frac{(1-f_{E2})}{(1-f_{E1})}$$ where K_{E1} and K_{E2} are the K_a's of formation of [$\mathbf{5}^{E1}$:glycoside] and [$\mathbf{5}^{E2}$:glycoside], respectively, and $f_{E1,E2} = \frac{[\mathbf{5}^{E1,E2}\text{:glycoside}]}{[\mathbf{5}^{E1,E2}]_0}$; $f_{E1,E2} = [\ \frac{\delta_{obs} - \delta_0}{\delta_c - \delta_0}\ ]^{E1,E2}$

$\delta_0 \equiv \delta_{\mathbf{5}}$; $\delta_c{}^{E1,E2} \equiv \delta[\mathbf{5}^{E1,E2}\text{:glycoside}]$

22. $$\frac{K_{\mathbf{5}^{E1}\text{:D-Glyc}}}{K_{\mathbf{5}^{E2}\text{:D-Glyc}}} = \frac{K_{\mathbf{5}^{E2}\text{:L-Glyc}}}{K_{\mathbf{5}^{E2}\text{:D-Glyc}}}$$

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